

REMARKS

Reconsideration of the subject application in view of the preceding amendments and the following remarks is respectfully requested.

Claims 1-37 and 60-84 are now pending in this application. In this amendment, Claims 1-3 and 5 have been amended to address formal deficiencies, and Claims 38-42, 44 and 46-59 have been withdrawn. Applicants reserve the right to pursue patent protection for the subject matter covered by any withdrawn or cancelled claims in another application claiming priority application from the present application. No new matter has been added to the subject application by this amendment, nor have any new issues been raised.

The Office Action

Per the outstanding Office Action, Claims 1-37 and 60-84 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. In short, at Page 2 and 3 of the outstanding office action, the Examiner argues that the term "highly viscous solution," as recited in Claims 1, 3 and 5, is a relative term, and that the term "reversibly solidified active substance," as recited in Claim 4, is not clear as to what substances it encompasses.

Claims 1-37 and 60-84 also stand rejected under 35 U.S.C. §103(a) as being purportedly unpatentable over U.S. Patent No. 5,981,719 to Woiszwilllo et al. (hereinafter

referred to as "Woiszwilllo"), U.S. Patent No. 4,822,535 to Ekman et al. (hereinafter referred to as "Ekman") in view of Laakso et al., Journal of Pharmaceutical Sciences, 1986;75(10):962-967 (hereinafter referred to as "Laakso") and U.S. Patent No. 5,622,657 to Takada et al. (hereinafter referred to as "Takada").

Response by Applicants

Applicants traverse the Examiner's rejections primarily because of the reasons set forth herein below. Applicants believe the claims as examined are directed to subject matter which is neither disclosed nor suggested by the cited references by themselves or in combination with any other references cited in the office action. By this amendment, Applicants have amended these claims in an effort to address the formal rejections included in the outstanding office action and advance prosecution, but not in acquiescence of any rejection thereto. Applicants respectfully submit that the claims as now presented are also directed to subject matter which is neither disclosed nor suggested by the cited references by themselves or in combination with any other references cited in the office action. Furthermore, Applicants believe these claims are now in condition for allowance. For illustrative purposes, Applicants have addressed the obviousness rejection in the outstanding office action as if the rejection had been asserted against the claims in their newly amended form.

Claim Rejections – 35 U.S.C. § 112

With regard to the 112 rejections, Applicants have amended claims 1-3 and 5 to obviate the rejection and render the claim definite. Applicants have not amended rejected claim 4 and instead point out that what is meant by the term "reversibly solidified" is included on page 7, paragraph [0066] of Applicants' specification. Thus, Applicants submit that the scope of Claim 4, and in particular, what the term "reversibly solidified active substance" encompasses would be clear to one of ordinary skill in the art, and respectfully request withdrawal of the rejection of claim 4.

Claim Rejections – 35 U.S.C. § 103

Applicants contend that the Examiner has not satisfied the burden necessary for establishing a *prima facie* case of obviousness, as alleged in the outstanding office action.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Woiszwillo discloses a method for producing microparticles wherein macromolecules are mixed with a soluble polymer or mixture of soluble polymers in the presence of an energy source such as heat for a predetermined length of time. microparticles containing an active substance with the objective of obtaining a stable slow release preparation. (See Col. 3, lines 22-28)

Ekman discloses a method of producing small, spherical polymer particles from systems containing two liquid phases, the one phase of which contains one or more dissolved substances and is dispersed in the form of small droplets in the other phase to form an emulsion, whereafter the droplets are caused to solidify. (See Col. 1, lines 5-11)

Woiszwillo states that it provides "a process for making microparticles that uses only aqueous or aqueous miscible solvents and does not utilize a water-in-oil emulsion in the manufacturing of the microparticles." (See Woiszwillo, Col. 4 lines 21-24) In contrast, Ekman states that its method, which is carried out with the use of a two-phase liquid system, is "characterized by using two mutually immiscible aqueous phases as the liquid phases." (See Ekman, Col. 1, lines 56-59)

The Courts have held that if the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959)

Clearly, the combination proposed by the Examiner involving Woiszwillo and Ekman would require changing the principle operation of these two references, since Woiszwillo prohibits using immiscible solvents and does not utilize a water-in-oil

emulsion in its process, while the method taught by Ekman necessitates the use of two immiscible liquids along with the formation of an emulsion.

The Courts have also held that if a proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984)

The proposed modification proffered by the Examiner involving Woiszwillo and Ekman attempts to combine conflicting teachings which would render both unsatisfactory for their respective intended purposes, since Woiszwillo's proscription against using immiscible solvents directly opposes Ekman's teaching which depends on the use of immiscible liquids. Clearly, two conflicting teachings can not be reconciled into one combined method. Presumably, even if such an unnatural combination was attempted, it would prove to be unfruitful and render both teachings unsatisfactory for their respective purposes.

Accordingly, there would have been no reason for one of ordinary skill in the art to prepare microparticles by employing a combination of the methods disclosed by Woiszwillo and Ekman, and no reasonable expectation of success. Applicants point out that it has been held that not only must there be some reasonable expectation of success in the references themselves to support a §103 rejection, but the prior art or surrounding circumstances must render the Applicants' claimed invention obvious to do rather than obvious to try. *In re Tomlinson*, 150 USPQ 623 (CCPA 1966). In this instance, Applicants contend that one skilled in the art would not find the presently claimed

invention obvious to do or try, in light of the fact that the cited references teach conflicting methods.

In addition, the Examiner improperly combines only portions of the references as support for a 103 rejection. The Federal Circuit has repeatedly warned against using the applicant's disclosure as a blueprint to reconstruct the claimed invention out of isolated teachings in the prior art. See, e.g., *Grain Processing Corp. v. American Maize-Products*, 840 F.2d 902, 907, 5 USPQ2d 1788, 1792 (Fed. Cir. 1988). Applicants point out that on Page 7, the Examiner argues that one of ordinary skill in the art would have been motivated to prepare the Applicants' claimed invention by employing the method of Woiszwillo followed by that of Ekman because Woiszwillo's method is to prepare a microparticle and then Ekman would further encapsulate such microparticle to increase the stability of the biological active substances. (Emphasis added).

Woiszwillo discloses microparticles which are stable and ready for a wide variety of commercial and research applications after being prepared according to the methods disclosed therein, including microparticles that exhibit sustained release of macromolecules for drug delivery. (See Woiszwillo, Col 13, line 20 to Col 16, line 30) Accordingly, there would be no reason or motivation for one skilled in the art to subject microparticles, which have been made ready for their intended end uses by the steps of Woiszwillo, to the further preparation steps disclosed by Ekman. It should be readily apparent that taking a microparticle in its end "ready for use" form and subjecting it to preparatory steps would be backwards and counterintuitive to one skilled in the art,

particularly since Ekman teaches a very different set of preparatory steps for preparing what conceivably might be microparticles intended for the same end use.

Even if all elements of a claim are disclosed in various prior art references, the claimed invention taken as a whole cannot be said to be obvious without some reason given in the prior art why one of ordinary skill would have been prompted to combine the teachings of the references to arrive at the claimed invention. *In re Regel*, 188 USPQ 132 (CCPA 1975). Applicants contend that the requisite motivation or reasoning to sustain this rejection can not be found in the cited references. One skilled in the art would recognize that the teachings of Woiszwillo and Ekman are not realistically combinable. Indeed, these references teach away from each other. Applicants contend that the requisite motivation to combine Woiszwillo and Ekman has not been established.

The one outstanding rejection relies on a combination of Woiszwillo, Ekman, Laakso and Takada. Since Woiszwillo and Ekman are not properly combinable to support a 103 rejection of the presently claimed invention, a combination which relies on a combination of Woiszwillo and Ekman, is also not properly combinable to support a 103 rejection of the presently claimed invention. Applicants contend that the burden for establishing a *prima facie* case of obviousness has not been met, and thus, the 103 rejection should clearly be withdrawn.

In addition, even if combined, the cited references do not disclose Applicants invention as now claimed in independent claim 1, namely, a process for producing parenterally administrable microparticles containing a biologically active substance, which process comprises:

- a) preparing an aqueous solution of the biologically active substance to be incorporated in the microparticles,
- b) mixing the solution obtained in step a) with an aqueous solution of polyethylene glycol to form a concentrated solution or solid particle precipitate of the biologically active substance,
- c) optionally washing the concentrated biologically active substance obtained in step b),
- d) mixing the concentrated biologically active substance obtained in step b) or c) with an aqueous starch solution,
- e) mixing the composition obtained in step d) with an aqueous solution of a polymer having the ability of forming a two-phase aqueous system, so as to form an emulsion of starch droplets which contain the biologically active substance as the inner phase in an outer phase of said polymer solution,
- f) causing or allowing the starch droplets obtained in step e) to solidify into starch microparticles,
- g) drying the starch microparticles from step f), and
- h) optionally applying a release controlling shell of a biocompatible and biodegradable polymer to the dried starch microparticles from step f).

Since the 103 rejection is improper, and independent claim 1 contains limitations which are neither taught nor suggested by the cited references, either alone or combined with any other references, these claims are neither rendered anticipated nor obvious. Furthermore, since the claims that depend from these independent claims provide further

limitations thereto, the dependent claims are also not rendered anticipated or obvious by the cited references, either alone or combined with any other references.

Accordingly, withdrawal of the rejections are therefore respectfully requested. It is respectfully submitted that as a result of this amendment and discussion relating thereto, all of the claims presently pending in this application, namely Claims 1-37 and 60-84 are in condition for allowance, and such action is earnestly solicited.

Conclusion

Applicant contends that the 103 rejection is improper and respectfully requests withdrawal of the same. Applicant believes the formal deficiencies have been addressed by this amendment and that all the 112 rejections should therefore be withdrawn also.

Accordingly, it is respectfully submitted that as a result of this amendment and discussion relating thereto, all of the claims presently pending in this application are in condition for allowance, and such action is earnestly solicited.

If the Examiner believes that a personal or telephonic interview may facilitate resolution of any remaining matters, Applicant's representative may be contacted at the number indicated below.

Respectfully submitted,



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